REMARKS

The present invention relates *inter alia* to methods for treating a subject in need of increased natriuretic peptide function. The methods comprise administering one or more inhibitors of prolyl-specific DPP to the subject in an amount sufficient to inhibit degradation of the natriuretic peptide.

Following entry of the foregoing amendments, claims 29-33 and 43-46 will be pending in the application. Claims 1-28 and 34-42 are cancelled without prejudice or disclaimer. The foregoing amendments to the prior pending claims and the new claims are fully supported by the specification as filed, and do not introduce new matter to the claims or necessitate a new search. Use of the present methods in subjects suffering from congestive heart failure is described in the specification, for example, in paragraph [0051], while the subject matter of new claims 43-46 is substantially the same as that of claims 29-33, with "B-type natriuretic peptide" replacing "natriuretic peptide."

Applicants respectfully request reconsideration of the claimed invention in view of the foregoing amendments and the following remarks.

Non-Art Based Remarks

1. Rejection of claims 29-33 under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 29-33 as allegedly failing to comply with the written description requirement of 35 U.S.C. § 112, first paragraph. Specifically, the Examiner contends that "none of the instant claims provides an amount of an inhibitor that would lend one of ordinary skill in the art to recognize as "sufficient" in preventing inhibition of a natriuretic peptide" and that "the specification does not link a specific amount with the said inhibitors that would be 'sufficient' to inhibit natriuretic peptide degradation." Office Action, page 5. Applicants respectfully traverse this rejection.

As an initial matter, Applicants note that this rejection, which is in the guise of a rejection under the written description requirement, appears to be questioning the enablement of the present invention. For example, whether or not one of skill in the art could "[determine] which one of the disclosed dosages in section 0136 to subscribe to which one of the disclosed DPP

inhibitors in section 0127" (Office Action, page 5) would appear to have no bearing on whether the specification reasonably conveys to the skilled artisan that the inventor was in possession of the claimed invention as of the filing date. *See, e.g., Ex parte Gupta and Lees*, 1996 WL 1806928 (Bd. Pat. App. & Interf.):

> We find this rejection for lack of "support" to be based on the written description requirement of § 112, first paragraph. . . . In order to make out a prima facie case of failure of the claims to comply with this section of the statute, the examiner must set forth "evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims." . . . Appellants submit that one of ordinary skill in this art would understand from the disclosure that "the amount of cure catalyst to be used is an amount 'effective to accelerate cure at the temperature employed coupled with the exemplified specific ranges that "any effective amount of cure catalyst of 'at least 0.01%' could be employed in the present invention" (brief, page 13). The examiner responds that "there is no substantiation for an amount of catalyst in excess of the 2.0%" and that one of ordinary skill in art "could not ascertain the maximum level ... because the broad description of 'amounts effective to accelerate cure' is contingent on the cure temperature which is not defined" (answer, pages 10-11).
>
> We must agree with appellants. . . . [that] whether one of ordinary skill in this art could "ascertain the maximum level" of cure catalyst is an issue arising under the enablement requirement of § 112, first paragraph, and has no bearing on whether that person would recognize in the disclosure a description of the invention defined by the claims.

The proper standard for determining compliance with the written description requirement of 35 U.S.C. § 112, first paragraph, is whether the specification reasonably conveys to the skilled artisan that the inventor was in possession of the claimed invention as of the filing date. *See* MPEP § 2163.02 (citing *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 227 USPQ 177, 179 (Fed. Cir. 1985)). The subject matter of the claimed invention need not be described literally in the specification in order to satisfy the requirements of 35 U.S.C. § 112, first paragraph. *Id.* An adequate written description "may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention." MPEP § 2163(II)(3)(a).

Applicants respectfully submit that, when properly applied, the present claims meet the written description standard.

In the present case, the invention does not lie in the identification of some previously unknown prolyl-specific dipeptidyl peptidase ("DPP") inhibitor, or some previously unknown method for delivery of such inhibitors to patients. As noted in the present specification (*e.g.*, in paragraphs [0126] and [0127]), and in the art cited by the Examiner (*e.g.*, Meester *et al.*, *Biochem. Pharmacol.* 54: 173-79 (1997)), the identity of prolyl-specific DPP inhibitors, the use of such inhibitors in subjects (to treat diabetes), and even appropriate concentrations of such inhibitors to be used to inhibit prolyl-specific DPP activity in subjects, are well known in the art. Indeed, numerous orally available prolyl-specific DPP inhibitors are well established in the art for treatment of diabetes, as the following list summarizes:

Company	**Prolyl-specific dipeptidyl peptidase inhibitor (clinical trial phase)**
Prosidion Limited	PSN9301 (phase 2)
Bristol-Myers Squibb Company	Saxagliptin / BMS-477118 (phase 3)
Eisai Co Ltd	E3024 (phase 1)
Eli Lilly & Co	TS-021 (phase 1)
Ferring Pharmaceuticals	FE-999011 (preclinical)
GlaxoSmithKline plc	815541 (phase 1)
GlaxoSmithKline plc	825964 (phase 1)
GlaxoSmithKline plc	Denagliptin/823093 (phase 2)
Glenmark Pharmaceuticals Ltd.	GRC-8087 (preclinical)
Glenmark Pharmaceuticals Ltd	GRC 8200 (phase 2)
Kyowa Hakko Kogyo Co., Ltd	K579 (preclinical)
Merck & Co Inc	Januvia/sitagliptin (post clinical trial, awaiting FDA action)
Novartis AG	LAF237/vildagliptin (post clinical trial, awaiting FDA action)
Ono Pharmaceutical Co., Ltd	ONO-5435/MK-0431 (post clinical trial, awaiting FDA action)
OSI Pharmaceuticals Inc	PSN9301(P93/01) (phase 2)
Phenomix Corporation	PHX1149 (phase 2)
Point Therapeutics Inc	PT-630 (preclinical)

Sanofi-Aventis	SSR 162329 (preclinical)
Sanofi-Aventis	SSR 162369 (phase 1)
Taisho Pharmaceutical Co Ltd	TS-021 (phase 1)
Takeda Pharmaceutical Company	SYR619 (preclinical)
Takeda Pharmaceutical Company	SYR322 (phase 3)
Tanabe Seiyaku Co., Ltd	TA-6666 (phase 2)
Torrent Pharmaceuticals, Ltd	TRC-8XXX (preclinical)

As described in detail in the specification, the present invention lies in identifying a new use of this well known class of compounds. Specifically, the present inventors discovered for the first time that such prolyl-specific DPP inhibitors find use in the context of congestive heart failure because natriuretic peptides such as B-type natriuretic peptide ("BNP") are substrates for hydrolysis by prolyl-specific DPPs.

Paragraph [0125] describes that increasing natriuretic peptide levels have been found to provide therapeutic benefit to heart failure patients. Indeed, NATRECOR® (human recombinant BNP) was approved by the U.S. FDA in 2001 for the intravenous treatment of patients with acutely decompensated congestive heart failure. Neutral endopeptidase ("NEP") has been considered to be a key degradation mediator of BNP, and inhibitors of NEP enzymatic activity have also found use in treating patients with heart failure. Moreover, a combination treatment with both BNP and NEP inhibitors has been reported to produce a synergistic effect on cardiac output, reduced vascular resistance, and unloading of the heart.

Human BNP, however, is unusually resistant to NEP degradation. *See, e.g.*, Smith *et al.*, "Delayed metabolism of human brain natriuretic peptide reflects resistance to neutral endopeptidase," *J. Endocrinol.* 167:239-46 (2000). This resistance led those in the art to question the role of neutral endopeptidase inhibition (*e.g.*, Smith *et al.*, page 245, last sentence) in the treatment of heart failure. Even after the filing date of the present invention, the identity of an alternative degradative pathway for BNP, while actively sought within the art, remained unknown. *See, e.g.*, Walther *et al.*, "Biochemical analysis of neutral endopeptidase activity reveals independent catabolism of atrial and brain natriuretic peptide," *Biol. Chem.* 385: 179-184 (2004):

> [O]ur data clearly indicate one or more other ANP- and BNP-degrading peptidases different from NEP at least in the heart, lungs, and kidneys. The nature of these peptidases is unknown until now, but they should not belong to the aminopeptidases and not be ACE, because bestatin and lisinopril did not influence NP [natriuretic peptide] degradation.

The present invention solves, at least in part, the search for alternative degradative pathways for natriuretic peptides in humans. As described in paragraph [0046], natriuretic peptides, and BNP specifically, contain penultimate proline residues, rendering the peptides suitable substrates for prolyl-specific DPPs. Pharmaceutically acceptable amounts of the various prolyl-specific DPP inhibitors known in the art, including those described in paragraphs [0126] and [0127] of the specification, may thus be used to inhibit this previously unknown degradative pathway for natriuretic peptides. Because of the relationship of natriuretic peptides, and BNP specifically, to heart failure, these methods may find particular application in the context of congestive heart failure as described in paragraph [0051] of the specification. As the various prolyl-specific DPP inhibitors known in the art can differ in terms of bioavailability, delivery route, half-life, *etc.*, precise dosages are left to the discretion of the skilled artisan. However, paragraph [0136] of the specification provides general guidance for selecting appropriate dosages.

In view of the foregoing, Applicants respectfully submit that the present specification reasonably conveys to the skilled artisan that the inventor was in possession of the claimed invention as of the filing date. Because 35 U.S.C. § 112, first paragraph demands no more, Applicants urge the Examiner to withdraw the written description rejection of claims 29-33.

Art Based Remarks

2. Information Disclosure Statement

The Examiner's comments that the IDS from January 24, 2005 which cited to a Notice of References Cited PTO-892 fails to include the proper application number is baffling. The PTO-892 form, listed as reference no. A8 on the SB-08 form contains a reference to serial no. 10/225,282, which serial number also appears on the PTO-892 form. The actual form PTO-892 is provided as a listed reference solely for completeness of the record. Applicants note that the individual references cited in the PTO-892 were separately listed on the SB-08 form and have

since been checked off by the Examiner. Accordingly, Applicant believes that there is no issue concerning the IDS filed January 24, 2005.

3. Rejection of claims 29, 30, and 32 under 35 U.S.C. § 102

Applicants respectfully traverse the rejection of claims 29, 30 and 32 under 35 U.S.C. § 102(b) as being anticipated by Meester *et al.*, *Biochem. Pharmacol.* 54: 173-79 (1997).

Meester *et al.* is cited for allegedly disclosing that intravenous injection of an inhibitor of prolyl-specific DPP "produced a prolonged inhibition of plasma DPP IV activity (i.e. sufficient to inhibit degradation of the natriuretic peptide)." Office Action, page 7.

Meester *et al.* does not disclose or otherwise suggest the use of such prolyl-specific DPP inhibitors in the context of congestive heart failure.

Applicants have amended the claims herein to recite a method comprising the following steps: *selecting a subject on the basis of a diagnosis of congestive heart failure*; and administering one or more inhibitors of prolyl-specific DPP to the subject in an amount sufficient to inhibit degradation of the natriuretic peptide. Because Meester *et al.* does not disclose the first of these steps, the cited publication does not anticipate the amended claims.

In view of the foregoing, Applicants urge the Examiner to withdraw the anticipation rejection of claims 29, 30, and 32.

4. Rejection of claims 29, 31, and 32 under 35 U.S.C. § 102

Applicants respectfully traverse the rejection of claims 29, 31 and 32 under 35 U.S.C. § 102(b) as being anticipated by Bergmann *et al.*, U.S. Patent 6,756,438.

Bergmann *et al.* is cited for allegedly disclosing the use of prolyl-specific DPP inhibitors in an amount sufficient to inhibit degradation of the natriuretic peptide for "therapeutically blocking dipeptidyl-aminopeptidase IV (DPP IV)." Office Action, page 7.

Bergmann *et al.* does not disclose or otherwise suggest the use of such prolyl-specific DPP inhibitors in the context of congestive heart failure.

Applicants have amended the claims herein to recite a method comprising the following steps: *selecting a subject on the basis of a diagnosis of congestive heart failure*; and

administering one or more inhibitors of prolyl-specific DPP to the subject in an amount sufficient to inhibit degradation of the natriuretic peptide. Because Bergmann *et al.* does not disclose the first of these steps, the cited publication does not anticipate the claims as amended.

In view of the foregoing, Applicants urge the Examiner to withdraw the anticipation rejection of claims 29, 31, and 32.

5. Rejection of claims 33 under 35 U.S.C. § 103

Applicants respectfully traverse the rejection of claim 33 under 35 U.S.C. § 102(b) as being unpatentable over Bergmann *et al.*, U.S. Patent 6,756,438, in view of Waeber *et al.*, U.S. Patent 4,839,343.

Bergmann *et al.* is cited for allegedly disclosing the use of prolyl-specific DPP inhibitors in an amount sufficient to inhibit degradation of the natriuretic peptide for "therapeutically blocking dipeptidyl-aminopeptidase IV (DPP IV)," and specifically "to patients suffering from sepsis or sepsis-like inflammation." Office Action, page 9. The Examiner acknowledges that Bergman *et al.* does not disclose co-administration of one or more additional molecules selected from the group consisting of inhibitors of neutral endopeptidase and natriuretic peptides. The Examiner turns to Waeber *et al.* for allegedly disclosing the use of neuropeptide Y (NPY) and peptide YY (PYY), which allegedly have natriuretic properties, "to prevent life-threatening hypotension due to septic shock. Office Action, page 9.

Neither Bergmann *et al.* nor Waeber *et al.* disclose or otherwise suggest the use of prolyl-specific DPP inhibitors, either alone or co-administration of one or more additional molecules selected from the group consisting of inhibitors of neutral endopeptidase and natriuretic peptides, in the context of congestive heart failure.

Applicants have amended the claims herein to recite a method comprising the following steps: *selecting a subject on the basis of a diagnosis of congestive heart failure*; and administering one or more inhibitors of prolyl-specific DPP to the subject in an amount sufficient to inhibit degradation of the natriuretic peptide. Because the cited publications, either considered alone or together, fail to disclose or suggest the first of these steps, no *prima facie* case of obviousness has been established.

In view of the foregoing, Applicants urge the Examiner to withdraw the obviousness rejection of claim 33.

CONCLUSION

Applicants respectfully submit that the pending claims are in condition for allowance. An early notice to that effect is earnestly solicited. Should any matters remain outstanding, the Examiner is encouraged to contact the undersigned at the address and telephone number listed below so that they may be resolved without the need for additional action and response thereto.

Respectfully submitted,

Date August 16, 2006

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